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THE JOURNAL OF IMMUNOLOGY

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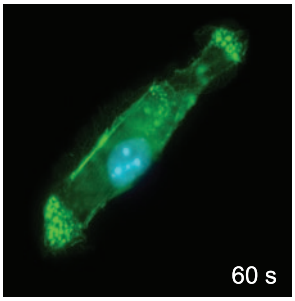
Sticking with Serotonin



Both mast cells and the neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) accumulate at sites of allergic inflammation. To date, there is no firm evidence of an influence of 5-HT on mast cell function. Kushnir-Sukhov et al. (p. 6422) determined that murine bone marrow-derived mast cells (mBMMCs) and human $CD34^+$-derived mast cells (huMCs) expressed mRNAs for several 5-HTRs. 5-HT did not induce mBMMC or huMC degranulation, did not have an effect on IgE-mediated degranulation, and did not alter protein phosphorylation or Ca^{2+} flux in activated cells; however, it did promote adhesion of mBMMCs and huMCs to fibronectin. $5\text{-HT}_{1A}R$ was identified by the ability of several specific 5-HTR antagonists to inhibit the adhesion activity and chemotaxis of mBMMCs and huMCs to 5-HT and by the inability of *5-HT*$_{1A}R^{-/-}$ mBMMCs to migrate in response to 5-HT or to adhere to fibronectin after exposure to 5-HT or to a specific $5\text{-HT}_{1A}R$ agonist. Cytoskeletal reorganization, including actin polymerization, was visualized by fluorescent toxin binding in mBMMCs treated with 5-HT. Mast cell accumulation in the dermis of wild-type mice at the site of 5-HT injection was not observed in *5-HT*$_{1A}R^{-/-}$ animals. The authors conclude that the presence of mast cells is a response to increased levels of 5-HT at sites of inflammation in mice and humans and propose that selective blockade of $5\text{-HT}_{1A}R$ could be useful in treating allergic inflammation.

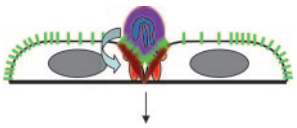
pIgR Defends against Giardia

The intestinal epithelium absorbs nutrients at the same time it employs secretory IgA (sIgA) and other host defenses to eliminate microbial pathogens. Although the highly conserved polymeric IgR (pIgR) transports sIgA into the intestinal lumen, a direct role for pIgR in defense against intestinal pathogens has not been shown. Davids et al. (p. 6281) found that *pIgR*$^{-/-}$, *IgA*$^{-/-}$, or J chain ($J^{-/-}$) mice were unable to clear the murine parasite *Giardia muris* from the small intestine by 7 wk postinfection, at which time, 40% of wild-type mice had cleared their infections. Mice heterozygous for *pIgR* had a 50% decrease in *pIgR* mRNA and in fecal IgA levels yet cleared their infections as efficiently as wild-type controls. In contrast, *pIgR*$^{-/-}$ or $J^{-/-}$, but not *IgA*$^{-/-}$, mice were able to clear infection with a strain of human *Giardia lamblia*. Fecal IgA levels in the *pIgR*$^{-/-}$ and $J^{-/-}$ mice infected with *G. lamblia* were ~10% of infected wild-type mice, but serum IgA in the *pIgR*$^{-/-}$ mice was elevated ~50-fold. The *pIgR*$^{-/-}$ immune serum was strongly antigiardial, provided passive immunity to mice infected with *G. lamblia*, and detected 12 conserved proteins on immunoblots of protein extracts from two *G. lamblia* strains; sera or breast milk from patients with giardiasis recognized most of the same proteins. The data indicate that pIgR is needed to eradicate intestinal lumenal *G. muris* requiring a lot of sIgA but not low levels of *G. lamblia* requiring much less sIgA.

Akt-ing to Prevent Tularemia

Macrophage apoptosis results when *Francisella tularensis*, the Gram-negative intracellular bacterium that causes tularemia, escapes from phagosomes and multiplies within the cytoplasm. Although inflammatory cytokines protect the host against infection, the macrophage intracellular signaling pathways involved are unknown. Rajaram et al. (p. 6317) detected phosphorylation of serine and threonine residues of Akt (protein kinase B) in mouse primary bone marrow macrophages and in an established macrophage cell line infected with a potent mouse strain, *Francisella novicida*. Proinflammatory cytokine production by the infected cells was reduced significantly, IL-10 production was greatly increased, and luciferase activity from a transfected NF-κB-driven reporter plasmid was decreased by prior treatment with an Akt inhibitor. A *F. novicida* mutant incapable of phagosomal escape induced enhanced levels of NF-κB and Akt activation and proinflammatory cytokine production in infected macrophages compared with the wild-type bacterium; IL-10 production was lower from mutant-infected cells. Infected mice expressing a constitutively active Akt transgene had greater survival than wild-type littermates. The experiments indicate that Akt activation in mouse macrophages infected with *F. novicida* induces NF-κB production of protective proinflammatory cytokines.

Ring around the Leukocyte



Leukocyte interactions with endothelial cells involve rolling, arrest, and transendothelial migration. Although endothelial cell ICAM-1 is involved in these events, the mechanism of cytoskeleton remodeling, necessary for transendothelial migration, has not been detailed. Using live cell imaging in an in vitro flow model, Yang et al. (p. 6440) detected ring-like structures comprised of a nonactivating fluorescent-labeled anti-ICAM-1 mAb and actin-GFP surrounding adherent polymorphonuclear leukocytes (PMNs) on TNF-α-activated HUVECs. Reduction of lateral mobility of ICAM-1 on the cell surface and formation of actin fibers after cross-linking the receptor with anti-ICAM-1 Ab were visualized by fluorescence recovery after photobleaching experiments and fluorescence microscopy, respectively; those responses did not occur in cells transfected with an ICAM-1 lacking its cytoplasmic domain. Activated HUVECs treated with a short interfering RNA for the multidomain scaffold protein cortactin had reduced actin-GFP fiber formation, less colocalization

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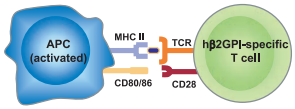
of cortactin-GFP with ICAM-1 in the ring-like structures, and fewer adherent PMNs. An inhibitor of src family kinases or expression of a mutant cortactin in which three tyrosine residues were mutated to phenylalanine also decreased actin-GFP fiber formation. Only PMNs with ICAM-1 ring-like clusters transmigrated. The authors present a model in which endothelial cell cortactin regulates ICAM-1 signaling and clustering, cytoskeletal remodeling, and leukocyte transmigration.

Epitope Spread in SLE

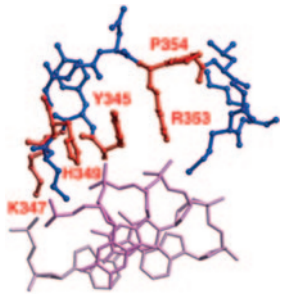


Systemic lupus erythematosus (SLE) is characterized by a gradual, ordered appearance of autoantibodies that can begin nearly a decade before development of clinical disease. Yet factors responsible for loss of self-tolerance and epitope spread of the autoimmune response are not known. On p. 6504, Levine et al. injected mice with human β2-glycoprotein I (β2GPI), an apoptotic cell-binding protein that is one of the first autoantigens targeted in SLE. Formation of anti-β2GPI Abs in response to soluble or apoptotic cell-bound protein was increased in mice coinjected with LPS; no Abs formed against murine β2GPI with or without LPS. LPS also elevated Ab responses to cardiolipin, several phospholipids, and lupus anticoagulant in β2GPI-injected mice. Whereas LPS alone increased the IgM response for β2GPI and cardiolipin, an increase in the IgG response required costimulation with LPS or TNF-α. This was confirmed by the inability of *CD28*$^{-/-}$ mice to develop IgG Abs to any of the proteins even with LPS. Autoantibody production in wild-type mice immunized with human β2GPI plus LPS spread to other autoantigens in a sequence characteristic of human SLE. The animals developed lupus nephritis and autoimmune hepatitis as shown by light and electron microscopy. The authors propose that the presentation of a single heterologous protein on an apoptotic cell scaffold containing multiple autoantigens promotes a long-lived T cell response that results in autoimmunity in mice through epitope spread.

Complexing IL-15

Cytokine IL-15 is transpresented by the α-chain of its receptor (IL-15Rα) to immune cells expressing the IL-15 β/common γ chain (IL-15Rβ/γC) complex. Augmenting the in vivo action of IL-15 would be beneficial to a variety of clinical conditions currently treated with the cytokine. Stoklasek et al. (p. 6072) found that CFSE-labeled splenic CD8$^+$ T, NK, NKT, and CD4$^+$ T cells transferred into congenic mice had much greater proliferation rates following injection with preformed IL-15/IL-15Rα-Fc complexes compared with controls receiving IL-15 alone. Proliferation of CD8$^+$ T cells was highest by 4 days posttreatment; IL-15 activity increased ~50-fold, and its serum half-life was extended from 1 to 20 h by complexing with IL-15Rα. *IL-15Rα*$^{-/-}$CD8$^+$ T cells adoptively transferred into *IL-15Rα*$^{-/-}$ hosts proliferated extensively in response to IL-15/IL-15Rα complexes; in contrast, *IL-15Rβ*$^{-/-}$CD8$^+$ T cells in wild-type hosts did not. IL-7 deficiency did not affect CD8$^+$ T cell proliferation, and naive and memory CD8$^+$ T cells had comparable levels of proliferation. Ag-specific lysis of CD8$^+$ T cells expressing a transfected viral Ag-specific TCR in IL-15/IL-15Rα complex-treated mice was as great as that in mice infected with the virus; memory CD8$^+$ T cells were induced by treatment with the complex even in the absence of Ag. Two treatments with IL-15/IL-15Rα complexes protected 90% of melanoma tumor-injected mice against tumor development, whereas only 10% of mice treated with PBS or IL-15 remained tumor free. The results demonstrate that an injected IL-15/IL-15Rα complex induces proliferation of effector and memory T cells by transpresentation to IL-15β/γC.

Importance of YxKxHxxxRP in GATA3



The zinc finger transcription factor, GATA binding protein 3 (GATA3), directs Th2 cell differentiation through two N-terminal transactivation domains and its N- and C-terminal zinc fingers. However, the function of an additional highly conserved region C-terminal to the second zinc finger is unknown. By transfection of GATA3 deletion mutants into CD4$^+$ T cells, Shinnakasu et al. (p. 5801) determined that aa 346–371 were essential for induction of IL-4, for *IL-5* or *IL-13* promoter activity, or for acetylation of Th2 cytokine gene loci as measured by intracellular staining, reporter assays, and chromatin immunoprecipitation assays, respectively. Four (aa 352–355) of the six residues were conserved in three human and mouse GATAs; aa 353–354 were found by alanine substitution mutation to be essential for GATA3 induction of IL-4-producing Th2 cells. Amino acid 353 was found to play a critical role and aa 354 an important role in GATA3 binding to DNA as measured by EMSA. Decreased DNA binding was detected for mutation of aa 345, aa 347, or aa 349. A motif similar to aa 352–355 between the N- and C-terminal zinc finger domains was found by an alanine substitution mutant to be required for transcription of the *IL-5* and *IL-13* promoters but not for histone modifications at Th2 cytokine gene loci; the second motif was only partially involved in DNA binding to GATA sequences. The authors present evidence for a crucial role in Th2 cell differentiation of a novel conserved amino acid motif YxKxHxxxRP (aa 345–354) adjacent to the C-terminal zinc finger domain of GATA3.

Summaries written by Dorothy L. Buchhagen, Ph.D.